Chris Baraniak Oct 4, 2022 7:00 AM

Scientists Have Discovered a New Set of Blood Groups

The 'Er' grouping could help doctors identify and treat some rare cases of blood incompatibility, including between pregnant mothers and fetuses.

The unborn baby was in trouble. Its mother's doctors, at a UK hospital, knew there was something wrong with the fetus's blood, so they decided to perform an emergency C-section many weeks before the baby was due. But despite this, and subsequent blood transfusions, the baby suffered a brain hemorrhage with devastating consequences. It sadly passed away.

It was not clear why the bleeding had happened. But there was a clue in the mother's blood, where doctors had noticed some strange antibodies. Sometime later, as the medics tried to find out more about them, a sample of the mother's blood arrived at a lab in Bristol run by researchers who study blood groups.

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They made a startling discovery: The woman's blood was of an ultrarare type, which may have made her baby's blood incompatible with her own. It is possible that this prompted her immune system to produce antibodies against her baby's blood—antibodies that then crossed the placenta and harmed her child, ultimately leading to its loss. It may seem implausible that such a thing could happen, but many decades ago, before doctors had a better understanding of blood groups, it was much more common.

Through studying the mother's blood sample, along with several others, scientists were able to unpick exactly what made her blood different, and in the process confirmed a new set of blood grouping—the "Er" system, the 44th to be described.

You are probably familiar with the 4 main blood types—A, B, O, and AB. But this is not the only blood classification system. There are many ways of grouping red blood cells based on differences in the sugars or proteins that coat their surface, known as antigens. The grouping systems run concurrently, so your blood can be classified in each—it might, for instance, be type O in the ABO system, positive (rather than negative) under the Rhesus system, and so on.

Thanks to differences in antigens, if someone receives incompatible blood from a donor, for example, the recipient's immune system may detect those antigens as foreign and react against them. This can be highly dangerous, and is why donated blood needs to be a suitable match if someone is having a transfusion.

On average, one new blood classification system has been described by researchers each year during the past decade. These newer systems tend to involve blood types that are mind-bogglingly rare but, for those touched by them, just knowing that they have such blood could be lifesaving. This is the story of how scientists unraveled the mystery of the latest blood system—and why it matters.

It was back in 1982 that researchers first described an unusual antibody in a blood sample that hinted that this mystery blood type was out there. The scientists could not go much further than that at the time, but they knew that the antibody was a clue pointing toward some unknown molecule or structure that prompted the person's immune system to generate it.

In the years that followed, more people with these unusual antibodies turned up—but only now and again. Generally, these people surfaced thanks to blood tests containing the mysterious and rare antibodies. Eventually, Nicole Thornton and her colleagues at NHS Blood and Transplant in the United Kingdom decided to investigate what might be behind the antibodies. "We work on rare cases," she says. "It starts off with a patient with a problem that we're trying to resolve."

But so rare were the mysterious antibodies in the latest work that when the team started their investigation, they had historical blood samples from just 13 people—gathered over 40 years—to analyze. Other recently established systems have been found thanks to similarly small numbers of people. Back in 2020, Thornton and her colleagues described a new blood group called MAM-negative that at the time was confirmed in just 11 people worldwide. And some of the most recently discovered blood groups have been found in single families, she adds. Both "MAM" and "Er" are obscure references to the names of the patients whose blood samples first sparked the possibility of a new blood group discovery.

It turns out that the new, 44th grouping system, detailed in the journal *Blood*, is tied to a particular protein found on the surface of red blood cells.

Originally, Thornton had an inkling this protein, called Piezo1, was involved after she compared the genomes of patients in the study. She and colleagues noticed how the gene responsible for this protein varies across people with different Er blood types. Due to those genetic differences, a small number of people have alternative amino acids, or building blocks, in their Piezo1 protein. Blood cells with the more common Piezo1 protein seem foreign to their bodies' immune systems as a result.

The team then checked to see whether antibodies reacted with lab cultures that either did or did not contain mutant versions of the Piezo1 protein, which they created using gene editing. That allowed them to confirm that variation in Piezo1 really was the driver of blood incompatibility in the people whose samples they were looking at. "It was something you couldn't have done a few years ago," says coauthor Ash Toye, professor of cell biology at the University of Bristol.

There are 5 Er antigens in total—5 possible variations of Piezo1 on the surface of red blood cells that can lead to incompatibility. 2 of the antigens were newly described by Thornton and her fellow researchers, and 1 of those was found in blood from the pregnant woman in the UK who lost her baby.

The results of the study will likely be officially ratified as defining a new blood group system later this year, at a meeting of the International Society of Blood Transfusion. The effort required to make the discovery was "massive," says Neil Avent, honorary professor in the blood diagnostics group at the University of Plymouth, who was not involved in the work. It also revealed complexities about this rare blood—for instance, that there are multiple genetic mutations associated with it.

Across the Atlantic, a separate team of researchers had also been trying to unravel the secrets of the new Er blood group, but were beaten by the British team. "That happens in this field," says Connie Westhoff of the New York Blood Center, who was part of the US research. "We often know that we're racing to find the solution in several different laboratories."

She says she and her colleagues have additional blood samples that appear to be from people with a rare Er blood group. And the research may not be over, she suggests—there are possibly more genetic mutations associated with this rare blood to uncover.

"Discovering a new blood group system is like discovering a new planet. It enlarges the landscape of our reality," says Daniela Hermelin at the Saint Louis University School of Medicine, who was not involved in the study. It adds to our knowledge of how blood incompatibility can affect pregnant mothers and their babies, she explains. And now that cases of blood incompatibility can potentially be attributed to the Er blood group, it increases the chance that doctors can correctly diagnose such a problem and treat it—by giving the baby a blood transfusion in the womb, for example.

It will also be possible to look out for and identify patients who have this troublesome blood. For example, someone might go to a hospital for a transfusion and have a preliminary blood test that reveals the presence of some unusual antibodies. Doctors could send the blood for analysis, and it might turn out that they have the rare Er blood described in the paper. "We have our testing set up to be able to do that," says Thornton. Rare blood might then be required for that person's transfusion, she adds. In the future, scientists in a lab might be able to grow red blood cells that could be offered to these patients for transfusion purposes.

It is very, very unlikely that you would have an incompatibility with someone else's blood due to Er antigens, says Avent. But "if you do, it's something you want to know about." https://www.wired.com/story/new-blood-types/